liver. By way of example, investigations using mice lacking GIPR and/or GLP-1R, as well as mice lacking DPP-4, showed involvement of GIP and GLP-1 in divergent biological activities. The results of these investigations point to involvement of GIP and GLP-1 in treating and/or preventing diabetes-related microvascular complications (e.g., retinopathy, nephropathy and neuropathy) and macrovascular complications (e.g., coronary artery disease, peripheral artery disease and cerebrovascular disease), as well as diabetes-related comorbidity (e.g., obesity, non-alcoholic fatty liver disease, bone fracture and cognitive dysfunction). See, e.g., Sieno at page 108.

SUMMARY

This disclosure features chemical entities (e.g., a compound or a pharmaceutically acceptable salt and/or hydrate and/or prodrug of the compound) that modulate (e.g., agonize or partially agonize or antagonize) glucagon-like peptide-1 receptor ("GLP-1R") and/or the gastric inhibitory polypeptide receptor ("GIPR"). The chemical entities are useful, e.g., for treating a subject (e.g., a human) having a disease, disorder, or condition in which modulation (e.g., agonism, partial agonism or antagonism) of GLP-1R and/or GIPR activities is benficial for the treatment or prevention of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition. In some examples, the modulation results in an enhancment of (e.g., an increase in) existing levels (e.g., normal or below normal levels) of GLP-1R and/or GIPR activity (e.g., signaling). In some examples, the chemical entities described herein further modulate (e.g., attenuate, uncouple) β-arrestin signaling relative to what is observed with the native ligand. This disclosure also features compositions as well as other methods of using and making the said chemical entities.

An "agonist" of GLP-1R includes compounds that, at the protein level, directly bind or modify GLP-1R such that an activity of GLP-1R is increased, e.g., by activation, stabilization, altered distribution, or otherwise relative to GLP-1R activity in absence of ligand.

Certain compounds described herein that agonize GLP-1R to a lesser extent (partial agonists) than a GLP-1R full agonist (e.g native GLP-1) can function in assays as antagonists as well as agonists. These compounds antagonize activation of GLP-1R by a GLP-1R full agonist because they prevent the full effect of GLP-1R interaction. However, the compounds also, on their own, activate some GLP-1R activity, typically less than a corresponding amount of the GLP-1R full agonist. Such compounds are sometimes referred to herein as "partial agonists of GLP-1R".

An “antagonist” of GLP-1R includes compounds that, at the protein level, directly bind or modify GLP-1R such that an activity of GLP-1R is decreased, e.g., by inhibition, blocking or dampening agonist-mediated responses, altered distribution, or otherwise relative to GLP-1R activity in absence of ligand.

In some examples, the compounds described herein are agonists (e.g. full agonists) of GLP-1R. In other examples, the compounds described herein are partial agonists or antagonists of GLP-1R.

An "agonist" of GIPR includes compounds that, at the protein level, directly bind or modify GIPR such that an activity of GIPR is increased, e.g., by activation, stabilization, altered distribution, or otherwise relative to GIPR activity in absence of ligand.

Certain compounds described herein that agonize GIPR to a lesser extent than native GIP (s full agonist) can function as antagonists as well as agonists. These compounds are partial antagonists as they reduce activation of GIPR by native GIPbecause they reduce the full effect of native GIP. However, the compounds also, on their own, activate some GIPR activity, typically less than a corresponding amount of native GIP. Such compounds are sometimes referred to herein as "partial agonists of GIPR".

An “antagonist” of GIPR includes compounds that, at the protein level, directly bind or modify GIPR such that an activity of GIPR is decreased, e.g., by inhibition, blocking or dampening agonist-mediated responses, altered distribution, or otherwise relative to GIPR activity in absence of ligand.

In some examples, the compounds described herein are agonists (e.g. full agonists) of GIPR. In other examples, the compounds described herein are partial

agonists of GIPR. In still other examples, the compounds described herein are or antagonists of GIPR.

In some examples, the compounds described herein are full agonists of both GLP-1R and GIPR. In some examples, the compounds described herein are partial agonists of both GLP-1R and GIPR. This disclosure also contemplates chemical entities that (i) agonize one of GLP-1R and GIPR (e.g., GLP-1R); and antagonize the other of GLP-1R and GIPR (e.g., GIPR). For example, this disclosure contemplates chemical entities that (i) fully agonize one of GLP-1R and GIPR (e.g., GLP-1R); and partially aginize or antagonize the other of GLP-1R and GIPR (e.g., GIPR). In certain examples, the chemical entities that are full agonists of GLP-1R and partial agonists or antagonists of GIPR; or that are partial agonists or antagonists of GLP-1R and full agonists of GIPR.

Generally, a receptor exists in an active (Ra) and an inactive (Ri) conformation. Certain compounds that affect the receptor can alter the ratio of Ra to Ri (Ra/Ri). For example, a full agonist increases the ratio of Ra/Ri and can cause a "maximal", saturating effect. A partial agonist, when bound to the receptor, gives a response that is lower than that elicited by a full agonist (e.g., an endogenous agonist). Thus, the Ra/Ri for a partial agonist is less than for a full agonist. However, the potency of a partial agonist may be greater or less than that of the full agonist.

In some examples, the chemical entities described herein further modulate (e.g., reduce, e.g., attenuate, disrupt, inhibit) β-arrestin coupling and/or b-arrestin signaling, and GLP-1R and/or GIPR internalization. In certain examples, the chemical entities described herein modulate (e.g., reduce, e.g., attenuate, disrupt, inhibit) recruitment of β-arrestin to a G-protein coupled receptor (e.g., GLP-1R). In certain examples, the chemical entities described herein modulate (e.g., reduce, e.g., attenuate, disrupt, inhibit) formation of a complex (“coupling”) (e.g., a signaling complex) between β-arrestin and a G-protein coupled receptor (e.g., GLP-1R or GIPR). The effects of the chemical entities described herein on β-arrestin signaling and associated downstream processes (e.g., those delineated above) can be assessed using conventional methods, e.g., PathHunter β-arrestin Assay for determining β-arresting coupling (see Examples section). By way of example,

a value of β-arrestin (GLP-1R) EC50 < 1 μM in the aforemented assay indicates a compound that induces β-arrestin recruitment to GLP-1R. GLP-1, the native ligand for GLP-1R, and therapeutic analogs thereof, such a liraglutide, are potent recruiters of β-arrestin. As another example, a value of β-arrestin (GLP1R) EC_{50} > 1 μM (e.g., > 10 μM) indicates a compound that does not substantially induce β-arrestin recruitment to GLP-1R. Therapeutic agents that modulate G-protein coupled receptors (e.g., GLP-1R and/or GIPR) can produce a variety of effects depending on the degree of cAMP activation versus β-arrestin -based signaling. It has been shown that b-arrestin coupling is a key strep in receptor internalization and subsequent de-sensitization and attenuation of signaling. Both GLP-1 (and the liraglutide analog) and GIP have been shown to produce rapid receptor internalization. Thus, compounds that activate GLP-1R and/or GIPR cAMP signaling but do not substantially couple to β-arrestin have the potential to prolong receptor signaling and extend pharmacological benefits. In some examples, the chemical entities described herein exhibit relatively strong GLP-1R and/or GIPR mediated cAMP activation with minimal or no detectable β-arrestin coupling. In some examples, the chemical entities described herein exhibit relatively strong GLP-1R mediated cAMP activation and no or little GIPR mediated cAMP activation with minimal or no detectable β-arrestin coupling.

In some examples, the compounds described herein show reduced activity in a rodent aversion model, while maintaining a relatively high potency in glucose clearance assay. Aversion models, such as conditioned taste aversion, are commonly used to identify compounds with adverse effects such as nausea. Nausea causing agents, such a Exendin-4 and liraglutide, are know to have a strong signal in conditioned taste aversion models.. Advantageously, some of the chemical entities described herein are therefore expected to have a reduced likelihood of producing unwanted side effects, such as nausea, when administered to a patient, while maintaining full pharmacological benefit.

Accordingly, in one example, this disclosure features peptide-based chemical entities (e.g., N-protected peptide-based chemical entities; e.g., peptide-based chemical entities

having from 30-50 amino acids, 30-45 amino acids, 30-40 amino acids, 35-40 amino acids; e.g., an N-protected peptide-based chemical entities having from 30-50 amino acids, 30-45 amino acids, 30-40 amino acids, 35-40 amino acids). The peptide-based chemical entities modulate (e.g., agonize or partially agonize or antagonize) glucagon-like peptide-1 receptor ("GLP-1R") and/or the gastric inhibitory polypeptide receptor ("GIPR") and optionally further modulate (e.g., uncouple, attenuate,) β-arrestin signaling and/or aversion as described herein.

In some examples, the peptide-based chemical entities agonize or partially agonize GLP-1R.

In some examples, the peptide-based chemical entities agonize or partially agonize or antagonize GIPR.

In some examples, said peptide-based chemical entities reduce (e.g., uncouple, attenuate, inhibit) β-arrestin signaling; e.g., reduce (e.g., uncouple, attenuate, inhibit) the recruitment of β-arrestin to a G-protein coupled receptor (e.g., GLP-1R); e.g., reduce (e.g., attenuate, disrupt, inhibit) the formation of a complex (e.g., a signaling complex) between β-arrestin and a G-protein coupled receptor (e.g., GLP-1R).

In certain examples, the peptide-based chemical entities:

- agonize or partially agonize GLP-1R;
- agonize or partially agonize or antagonize GIPR;
- reduce (e.g., uncouple, attenuate, inhibit) β-arrestin signaling; e.g., reduce (e.g., attenuate, disrupt, inhibit) the recruitment of β-arrestin to a G-protein coupled receptor (e.g., GLP-1R and/or GIPR); e.g., reduce (e.g., attenuate, disrupt, inhibit) the formation of a complex (e.g., a signaling complex) between β-arrestin and a G-protein coupled receptor (e.g., GLP-1R and/or GIPR); and
- stimulate glucose clearance in vivo (GTT test) without causing aversion.

In some examples, the peptide-based chemical entities exhibit a value of cAMP (GLP1R) EC50 of less than about 10 nM, 5 nM, or 1 nM (e.g., less than about 1 nM).

In some examples, the peptide-based chemical entities exhibit a value of cAMP (GIPR) EC50 of less than about 100 nm, 50 nM, or 10 nM (e.g., less than about 10 nM).

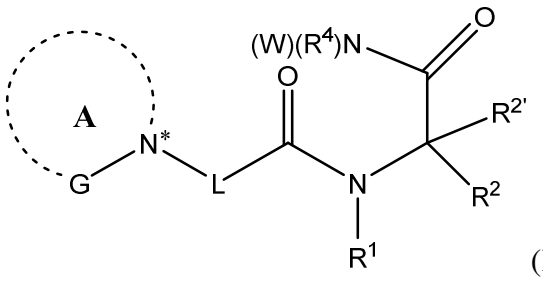
In some examples, the peptide-based chemical entities inhibit GIP induced cAMP production (GIPR antagonism).

In some examples, the compounds described herein exhibit a value of β-arrestin (GLP1R) EC50 > 1 μM.

In some examples, the peptide-based chemical entities:

- exhibit a value of cAMP (GLP1R) EC50 of less than about 10 nM, 5 nM, or 1 nM (e.g., less than about 1 nM);
- exhibit a value of cAMP (GIPR) EC50 of less than about 100 nm, 50 nM, or 10 nM (e.g., less than about 10 nM) or are GIPR antagonists;
- exhibit a value of β-arrestin (GLP1R) EC50 > 1 μM; and
- stimulate glucose clearance in vivo (GTT test) without causing aversion (nausea)

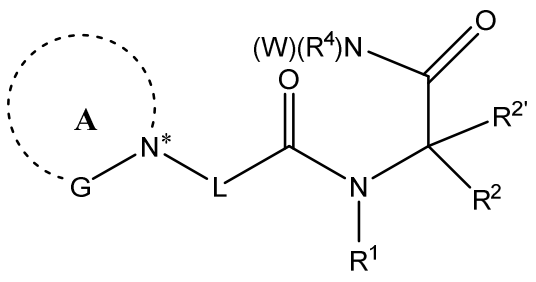
In one example, the featured peptide-based chemical entities include compounds of Formula (IAA), or a pharmaceutically acceptable salt thereof:



(IAA)

in which ring **A**, **G**, **L**, **W**, **R^1**, **R^2**, **R$^{2'}$**, and **R^4** can be as defined anywhere herein.

In one aspect, the present disclosure refers to a compound having formula (IAA), or a pharmaceutically acceptable salt thereof:



(IAA)

wherein:

ring A is:

(**i**) a saturated or unsaturated monocyclic ring that includes from 3-8 ring atoms (inclusive of **G** and the nitrogen atom labelled N*); or

(**ii**) a saturated or unsaturated bicyclic or tricyclic ring that includes from 6-14 ring atoms (inclusive of **G** and the nitrogen atom labelled N*), wherein:

- **G** is C(O), S(O), or SO_2; and
- the dotted, circular line connecting **G** and N* is a divalent group that includes from 1-6 ring atoms; wherein:

(**a**) from 0-2 of the divalent group's ring atoms are ring heteroatoms, which are each independently selected from the group consisting of N, N(**R**^{a}), O, S, and SO_2; and

(**b**) from 1-6 of the divalent group's ring atoms are ring carbon atoms, which are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b;

wherein:

(**1**) when **ring A** is a monocyclic ring, then each of the divalent group's 1-6 ring carbon atoms is independently selected from the group consisting of CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b; and

(**2**) when **ring A** is a bicyclic or tricyclic ring, then (**A**) or (**B**) applies:

(**A**) two or three adjacent ring carbon atoms of the divalent group are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$,

and CHR^b and are fused to a second ring that is selected from the group consisting of:

(**a**) C_{6-10} aryl optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**b**) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected $\mathbf{R^c}$;

(**c**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**d**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$; or

(**B**) one of the divalent group's ring carbon atoms is C and is spiro-fused to a second ring that is selected from the group consisting of:

(**a**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**b**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

L is:

(**i**) $-(CH_2)_{\mathbf{m}}-\mathbf{X^1}-(CH_2)_{\mathbf{n}}-\mathbf{X^2}-(CH_2)_{\mathbf{p}}-$ (formula VIII), wherein **m** is from 1-6; **n** is from 0-2; and **p** is from 0-8;

(**ii**) $-C(O)-(CH_2)_{\mathbf{n}}-\mathbf{X^3}-(CH_2)_{\mathbf{p}}-$ (formula IX), wherein **n** is from 0-2; and **p** is from 0-8;

(**iii**) $-(CH_2)_{\mathbf{q}}-$, wherein **q** is from 1-10;

(**iv**) -C(O)-; or

(**v**) -$(CH_2)_{\mathbf{m}}$-$\mathbf{X^1}$ -$(CH_2)_{\mathbf{p}}$- (formula VIII), wherein **m** is from 1-6; and **p** is from 0-8;

$\mathbf{X^1}$ is -C(O)-; -N(R')C(O)-; -C(O)N(R')-; or -N(R')C(O)NR')-; wherein each occurrence of **R'** is independently selected from the group consisting of: H and C_{1-4} alkyl;

$\mathbf{X^2}$ is:

(**i**) -O-;

(**ii**) -S-;

(**iii**) -$S(O)_t$-, wherein **t** is 1 or 2;

(**iv**) -$C(Q^1)(Q^2)$-, wherein each of $\mathbf{Q^1}$ and $\mathbf{Q^2}$ is independently selected from the group consisting of H and C_{1-4} alkyl; or $\mathbf{Q^1}$ and $\mathbf{Q^2}$, together with the carbon atom to which each is attached forms C_{3-10} cycloalkyl that is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$ and optionally fused to phenyl;

(**v**) C_{6-10} arylene optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vi**) heteroarylene including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vii**) C_{3-10} cycloalkylene optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**viii**) heterocycloalkylene including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^d}$;

(**ix**) C_2-C_4 alkenylene optionally substituted with from 1-2 $\mathbf{R^e}$; or

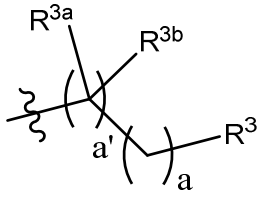
(**x**) C_2-C_4 alkynylene optionally substituted with from 1-2 $\mathbf{R^e}$;

$\mathbf{X^3}$ is: -O-; -S-; or -$S(O)_t$-, wherein **t** is 1 or 2;

each of $\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^4}$ is independently selected from the group consisting of H and unsubstituted C_{1-3} alkyl;

R$^{2'}$ is as defined according to **(AA)** or **(BB)** below:

(AA)



R$^{2'}$ is , wherein:

R^{3} is -C(O)OH, -C(O)OR^{31}, -CH(C(O)OH)$_2$ or a carboxylic acid isostere (e.g., amide or tetrazolyl);

a is 0-5;

a' is 0 or 1; and

each of **R^{3a}** and **R^{3b}** is independently H or C$_{1-3}$ alkyl;

(BB)

R$^{2'}$ and **R^{4}** taken together with the atoms connecting them form a ring including from 5-8 ring atoms, wherein from 3-7 are ring carbon atoms each substituted with from 1-2 substituents independently selected from H, halo, hydroxy, oxo, and C$_{1-3}$ alkyl; and from 0-1 is a heteroatom (in addition to the N attached to **R^{1}**) selected from O, -NH, -N(C$_{1-3}$ alkyl), and S (e.g., R^4 and R^3, taken together with the atoms to which each is attached form a ring including 5-8 ring atoms);

R^{31} is:

(**i**) C$_{1-6}$ alkyl optionally substituted with from 1-2 independently selected **R^{e}**;

(**ii**) -(C$_{0-3}$ alkylene)-C$_{3-10}$ cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1-4 independently selected **R^{d}**;

(**iii**) -(C$_{0-3}$ alkylene)-heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N(**R^{a}**), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected **R^{d}**;

(**iv**) -(C_{0-3} alkylene)-C_{6-10} aryl, wherein the aryl is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$; or

(**v**) -(C_{0-3} alkylene)-heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected $\mathbf{R^c}$;

each occurrence of $\mathbf{R^a}$ is independently selected from the group consisting of: H; C_{1-4} alkyl; C_{3-6} cycloalkyl; -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); and -$S(O)_{1-2}$(C_{1-6} alkyl);

each occurrence of $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{R^{31}}$; C_{1-4} haloalkyl; –OH; oxo; -F; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)(C_{1-4} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -$S(O)_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of $\mathbf{R^c}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$; C_{3-6} cycloalkyl; C_{1-4} haloalkyl; –OH; -halo; -NO_2; N_3; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} thioalkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -$S(O)_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$; C_{1-4} haloalkyl; –OH; -F; Cl; -N(R^a)(R''); oxo; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -$S(O)_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of $\mathbf{R^e}$ is independently selected from the group consisting of: –OH; - -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of **R**", **R**"', and **R**"" is independently selected from the group consisting of: H and C_{1-6} alkyl; and

W is a peptide having the formula W'-R^5, wherein **W'** is a sequence of from 5-60 amino acids, and $\mathbf{R^5}$ is a C-terminal amino acid, amino acid ester, or amino acid amide that is optionally substituted with from 1-2 modifying groups (e.g., 1-2 groups selected from an acyl group and a PEG group); and

provided that one or more of the compound provisions delineated herein apply.

In one example, pharmaceutical compositions are featured that include a chemical entity described herein (e.g., a compound described generically or specifically herein or a

pharmaceutically acceptable salt thereof or compositions containing the same) and one or more pharmaceutically acceptable excipients. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound or salt as described herein and one or more pharmaceutically acceptable excipients.

In one example, methods for modulating (e.g., agonizing, partially agonizing, or antagonizing) GLP-1R and/or GIPR activities are featured that include contacting GLP-1R and/or GIPR with a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). Methods include *in vitro* methods, e.g., contacting a sample that includes one or more cells, each independently comprising one or more of GLP-1R and/or GIPR with the chemical entity. Methods can also include *in vivo* methods; e.g., administering the chemical entity to a subject (e.g., a human) having a disease, disorder, or condition in which modulation of GLP-1R and/or GIPR signaling is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition (e.g., diabetes; e.g., NASH; e.g., obesity). *In vivo* methods include, but are not limited to modulating (e.g., increasing) insulin levels and modulating (e.g., decreasing) glucose levels in a subject (e.g., a human). In some of the foregoing examples, said methods of modulating are achieved without substantially stimulating β-arrestin signaling; e.g., without stimulating the recruitment of β-arrestin to a G-protein coupled receptor (e.g., GLP-1R); e.g., without stimulating the formation of a complex (e.g., a signaling complex) between β-arrestin and a G-protein coupled receptor (e.g., GLP-1R). In some of the foregoing examples, said methods of modulating are achieved without causing aversion or nausea.

In one aspect, the present disclosure refers to an *in vitro* method for modulating GLP-1R and/or GIPR activity, the method comprising contacting GLP-1R and/or GIPR with a compound as described herein. In another aspect, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for modulating GLP-1R and/or GIPR activity *in vivo*.

In one aspect, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for modulating GLP-1R and/or GIPR induced aversion, nausea and/or vomiting.

In one aspect, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for modulating (e.g., increasing) insulin levels in a subject in need of such modulating.

In one aspect, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for modulating (e.g., decreasing) glucose levels in a subject in need of such modulating.

In one aspect, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for treating a disease, disorder, or condition, in which modulating GLP-1R and/or GIPR signaling can alter the pathology and/or symptoms and/or progression of the disease, disorder, or condition.

In one aspect, the present disclosure refers to use of a compound as described herein in the manufacture of a medicament for treating a disease, disorder, or condition, in which modulating GLP-1R and/or GIPR signaling causes aversion, nausea or vomiting.

In a further example, methods of treatment of a disease, disorder, or condition are featured, in which modulation of GLP-1R and/or GIPR signaling is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition. The methods include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein, a pharmaceutically acceptable salt thereof, or compositions containing the same).

In another example, this disclosure features methods of treating a subject having a disease, disorder, or condition in which modulation of GLP-1R and/or GIPR signaling is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition. The methods include administering a chemical entity described herein (e.g., a compound described generically or specifically herein, a pharmaceutically acceptable salt thereof or compositions containing the same) in an amount effective to treat the disease, disorder, or condition.

In a further example, methods of treatment are featured that include administering to a subject chemical entity described herein (e.g., a compound described generically or specifically herein, a pharmaceutically acceptable salt thereof, or compositions containing the same). The methods include administering the chemical entity in an amount effective to treat a disease, disorder, or condition, wherein modulation of GLP-1R and/or GIPR is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition, thereby treating the disease, disorder, or condition.

In another example, methods of treatment can further include:

(**i**) administering a first therapeutic agent that modulates (e.g., agonizes, partially agonizes, or antagonizes) GLP-1R and/or GIPR to a subject as defined anywhere herein;

(**ii**) determining that the subject is suffering from one or more side effects (e.g., aversion, nausea or vomiting); and

(**iii**) ceasing administration of the first therapeutic agent and administering a chemical entity as described herein (e.g., a compound having formula (IAA), (IA), or (I)).

Non-limiting examples of such diseases, disorders, and conditions include metabolic syndrome; diabetes (e.g., type 2 diabetes); obesity; obesity-related disorders; impaired glucose tolerance; insulin resistance; non-alcoholic steatohepatitis (NASH); fatty liver disease; steatohepatitis; and other forms of inflammation in metabolically important tissues including, liver, fat, pancreas, kidney, and gut.

Other non-limiting examples of such diseases, disorders, and conditions include neurological disorders include brain insulin resistance, mild cognitive impairment (MCI), Alzheimer's disease (AD), Parkinson's disease (PD), anxiety, dementia (e.g., senile dementia), traumatic brain injury, Huntington's chores, tardive dyskinesia, hyperkinesia, mania, Morbus Parkinson, steel-Richard syndrome, Down's syndrome, myasthenia gravis, nerve trauma, brain trauma, vascular amyloidosis, cerebral hemorrhage I with amyloidosis, brain inflammation, Friedrich's ataxia, acute confusion disorder, amyotrophic lateral sclerosis (ALS), glaucoma, and apoptosis-mediated degenerative diseases of the central nervous system (e.g., Creutzfeld-Jakob Disease, bovine spongiform encephalopathy (mad cow disease), and chronic wasting syndrome).

Still other non-limiting examples of such diseases, disorders, and conditions include bone disorder characterized by altered bone metabolism, such as osteoporosis, including post-menopausal osteoporosis, poor bone strength, osteopenia, Paget's disease, osteolytic metastasis in cancer patients, osteodistrophy in liver disease and the altered bone metabolism caused by renal failure or haemodialysis, bone fracture, bone surgery, aging, pregnancy, protection against bone fractures, and malnutrition.

In certain examples, the disease, disorder, or condition is diabetes.

In other examples, the disease, disorder, or condition is NASH.

In still other examples, the disease, disorder, or condition is obesity.

In other examples, the disease, disorder, or condition is Alzheimer's disease (AD) or Parkinson's disease (PD).

In still other examples, the disease, disorder, or condition is a bone disorder characterized by altered bone metabolism, such as osteoporosis, including post-menopausal osteoporosis, poor bone strength, osteopenia, Paget's disease, osteolytic metastasis in cancer patients, osteodistrophy in liver disease and the altered bone metabolism caused by renal failure or haemodialysis, bone fracture, bone surgery, aging, or pregnancy.

In certain examples, the chemical entities described herein are useful for protection against bone fractures.

The methods described herein can further include treating one or more conditions associated, co-morbid or sequela with any one or more of the conditions described herein. By way of non-limiting example, the methods can further include treating one or more conditions that are co-morbid or sequela with diabetes (e.g., type 2 diabetes), such as obesity, obesity-related disorders, metabolic syndrome, impaired glucose tolerance; insulin resistance; cardiovascular risk factors. (e.g., coronary artery disease, peripheral artery disease, cerebrovascular disease, hypertension, and risk factors related to unmanaged cholesterol and/or lipid levels, and/or inflammation), retinopathy, nephropathy, neuropathy, NASH, bone fracture and cognitive dysfunction.

In another example, this disclosure features methods for screening a candidate compound for treatment of a disease, disorder, or condition, in which modulation of GLP-1R and/or GIPR is beneficial for the treatment of the underlying pathology and/or symptoms and/or progression of the disease, disorder, or condition; the method comprising:

(**a**) contacting the candidate compound with (**i**) a β-Arrestin-coupled GPCR receptor signaling complex or (**ii**) one or more GPCR receptor signaling complexes that are not complexed with β-arrestin (e.g., uncoupled GLP-1R and/or uncoupled GIPR); and

(**b**) detecting (**i**) the disruption of the b-arrestin coupled complex; or (**ii**) detecting the formation of the signaling complex in the absence of b-arrestin coupling; wherein the candidate compound modulates (e.g., agonizes, partially agonizes,) GLP-1R and/or GIPR.

In certain examples, the methods further include selecting a candidate compound that exhibits a value of β-arrestin (GLP-1R) EC50 > 1 μM.

The methods can further include identifying the subject.

The methods can further include administering one or more other therapeutic agents (e.g., in combination with a chemical entity described herein).

Examples can include one of more of the following advantageous properties.

In some examples, the compounds described herein exhibit a value of AUC Score of 0-25% of vehicle, which corresponds to a finding of maximal decrease in glucose excursion compared to control.

In some examples, the compounds described herein exhibit a value of cAMP (GLP-1R) EC50 of less than about 1 nM, which is indicative that the compound is a relatively potent GLP-1R agonist.

In some examples, the compounds described herein exhibit a value of cAMP (GLP-1R) Emax of greater than about 80%, which is indicative that the compound is an agonist that can fully activate GLP-1R.

In some examples, the compounds described herein exhibit a value of cAMP (GIPR) EC_{50} of less than about 10 nM, which is indicative that the compound is a relatively potent GIPR agonist.

In some examples, the compounds described herein exhibit a value of cAMP (GIPR) EC_{50} of less than about 10 nM, which is indicative that the compound is a relatively potent GIPR antagonist.

GLP-1 and GIP are susceptible to rapid degradation by dipeptidyl peptidease-IV (DPP-IV) (see, e.g., Deacon, et al. Journal of Clinical Endocrinology & Metabolism, 1995, 80, 952-957). As such, GLP-1 and GIP have been shown to exhibit relatively short half-life times in human due to DPP-IV degradation. Advantageously, the compounds described herein exhibit relatively long half-life times in the presence of DPP-IV when compared to those of GLP-1 and GIP.

In some examples, the compounds described herein exhibit a value of β-arrestin coupling (GLP-1R) EC50 > 1 μM in a β-arrestin (GLP1R) assay that measures the formation of a complex between GLP-1R and β-arrestin in cells. A value of β-arrestin (GLP1R) EC50 > 1 μM indicates a compound that does not substantially induce β-arrestin recruitment to GLP-1R.

In some examples, the compounds described herein exhibit a value of conditioned taste aversion ("CTA") = 0.6-1.0, which indicates no measurable aversion to a compound, which is desired. A value of CTA = 0.0-0.6 indicates significant aversion to

a compound. The conditioned taste aversion assay measures the preference for a dilute saccharin solution that is associated with compound administration.

In some examples, the compounds described herein have a reduced likelihood of producing unwanted side effects when administered to a patient. A non-limiting example of such a side effect is nausea.

Other examples include those described in the Detailed Description, drawings, and/or in the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 depicts representative compounds of Formula (IAA).

Additional Definitions

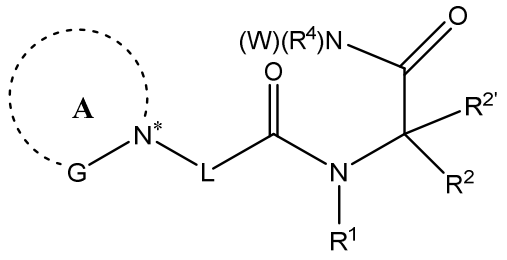
To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties.

As used herein, the term "GLP-1R" is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and antisense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, homologous and/or orthologous GLP-1R molecules, isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

As used herein, the term "GIPR" is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and antisense polynucleotide strands,

WHAT IS CLAIMED IS:

1. A compound having formula (IAA), or a pharmaceutically acceptable salt thereof:



(IAA)

wherein:

ring A is:

(**i**) a saturated or unsaturated monocyclic ring that includes from 3-8 ring atoms (inclusive of **G** and the nitrogen atom labelled N*); or

(**ii**) a saturated or unsaturated bicyclic or tricyclic ring that includes from 6-14 ring atoms (inclusive of **G** and the nitrogen atom labelled N*), wherein:

- **G** is C(O), S(O), or SO_2; and
- the dotted, circular line connecting **G** and N* is a divalent group that includes from 1-6 ring atoms; wherein:

(**a**) from 0-2 of the divalent group's ring atoms are ring heteroatoms, which are each independently selected from the group consisting of N, N(**R**^{a}), O, S, and SO_2; and

(**b**) from 1-6 of the divalent group's ring atoms are ring carbon atoms, which are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b;

wherein:

(**1**) when **ring A** is a monocyclic ring, then each of the divalent group's 1-6 ring carbon atoms is independently selected from the group consisting of CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b; and

(**2**) when **ring A** is a bicyclic or tricyclic ring, then (**A**) or (**B**) applies:

(**A**) two or three adjacent ring carbon atoms of the divalent group are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b and are fused to a second ring that is selected from the group consisting of:

(**a**) C_{6-10} aryl optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**b**) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected $\mathbf{R^c}$;

(**c**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**d**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$; or

(**B**) one of the divalent group's ring carbon atoms is C and is spiro-fused to a second ring that is selected from the group consisting of:

(**a**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**b**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

L is:

(**i**) $-(CH_2)_{\mathbf{m}}-\mathbf{X^1}-(CH_2)_{\mathbf{n}}-\mathbf{X^2}-(CH_2)_{\mathbf{p}}-$ (formula VIII), wherein **m** is from 1-6; **n** is from 0-2; and **p** is from 0-8;

(**ii**) $-C(O)-(CH_2)_{\mathbf{n}}-\mathbf{X^3}-(CH_2)_{\mathbf{p}}-$ (formula IX), wherein **n** is from 0-2; and **p** is from 0-8;

(**iii**) $-(CH_2)_{\mathbf{q}}-$, wherein **q** is from 1-10;

(**iv**) -C(O)-; or

(**v**) $-(CH_2)_{\mathbf{m}}-\mathbf{X^1}-(CH_2)_{\mathbf{p}}-$ (formula VIII), wherein **m** is from 1-6; and **p** is from 0-8;

$\mathbf{X^1}$ is -C(O)-; -N(R')C(O)-; -C(O)N(R')-; or -N(R')C(O)NR')-; wherein each occurrence of $\mathbf{R'}$ is independently selected from the group consisting of: H and C_{1-4} alkyl;

$\mathbf{X^2}$ is:

(**i**) -O-;

(**ii**) -S-;

(**iii**) -$S(O)_t$-, wherein **t** is 1 or 2;

(**iv**) -$C(Q^1)(Q^2)$-, wherein each of $\mathbf{Q^1}$ and $\mathbf{Q^2}$ is independently selected from the group consisting of H and C_{1-4} alkyl; or $\mathbf{Q^1}$ and $\mathbf{Q^2}$, together with the carbon atom to which each is attached forms C_{3-10} cycloalkyl that is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$ and optionally fused to phenyl;

(**v**) C_{6-10} arylene optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vi**) heteroarylene including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vii**) C_{3-10} cycloalkylene optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**viii**) heterocycloalkylene including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^d}$;

(**ix**) C_2-C_4 alkenylene optionally substituted with from 1-2 $\mathbf{R^e}$; or

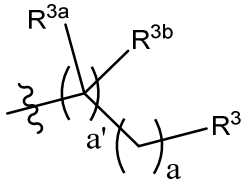
(**x**) C_2-C_4 alkynylene optionally substituted with from 1-2 $\mathbf{R^e}$;

$\mathbf{X^3}$ is: -O-; -S-; or -$S(O)_t$-, wherein **t** is 1 or 2;

each of $\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^4}$ is independently selected from the group consisting of H and unsubstituted C_{1-3} alkyl;

$\mathbf{R^{2'}}$ is as defined according to **(AA)** or **(BB)** below:

(AA)

$\mathbf{R^{2'}}$ is 

, wherein:

$\mathbf{R^3}$ is -C(O)OH, -$C(O)OR^{31}$, -$CH(C(O)OH)_2$ or a carboxylic acid isostere (e.g., amide or tetrazolyl);

a is 0-5;

a' is 0 or 1; and

each of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is independently H or C_{1-3} alkyl;

(BB)

$\mathbf{R^{2'}}$ and $\mathbf{R^4}$ taken together with the atoms connecting them form a ring including from 5-8 ring atoms, wherein from 3-7 are ring carbon atoms each substituted with from 1-2 substituents independently selected from H, halo, hydroxy, oxo, and C_{1-3} alkyl; and from 0-1 is a heteroatom (in addition to the N attached to $\mathbf{R^1}$) selected from O, -NH, -N(C_{1-3} alkyl), and S (e.g., R^4 and R^3, taken together with the atoms to which each is attached form a ring including 5-8 ring atoms);

$\mathbf{R^{31}}$ is:

(**i**) C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$;

(**ii**) -(C_{0-3} alkylene)-C_{3-10} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iii**) -(C_{0-3} alkylene)-heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iv**) -(C_{0-3} alkylene)-C_{6-10} aryl, wherein the aryl is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$; or

(**v**) -(C_{0-3} alkylene)-heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected $\mathbf{R^c}$;

each occurrence of $\mathbf{R^a}$ is independently selected from the group consisting of: H; C_{1-4} alkyl; C_{3-6} cycloalkyl; -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); and -S(O)$_{1-2}$(C_{1-6} alkyl);

each occurrence of $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{R^{31}}$; C_{1-4} haloalkyl; –OH; oxo; -F; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)(C_{1-4} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of $\mathbf{R^c}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$; C_{3-6} cycloalkyl; C_{1-4} haloalkyl; –OH; -halo; $-NO_2$; N_3; $-N(R^a)(R'')$; C_{1-4} alkoxy; C_{1-4} thioalkoxy; C_{1-4} haloalkoxy; $-OC(=O)(C_{1-6}$ alkyl); $-C(=O)(C_{1-6}$ alkyl); $-C(=O)O(C_{1-6}$ alkyl); -C(=O)OH, $-C(=O)N(R''')(R'''')$, $-S(O)_{1-2}(C_{1-6}$ alkyl); and cyano;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$; C_{1-4} haloalkyl; –OH; -F; Cl; $-N(R^a)(R'')$; oxo; C_{1-4} alkoxy; C_{1-4} haloalkoxy; $-OC(=O)(C_{1-6}$ alkyl); $-C(=O)(C_{1-6}$ alkyl); $-C(=O)O(C_{1-6}$ alkyl); -C(=O)OH, $-C(=O)N(R''')(R'''')$, $-S(O)_{1-2}(C_{1-6}$ alkyl); and cyano;

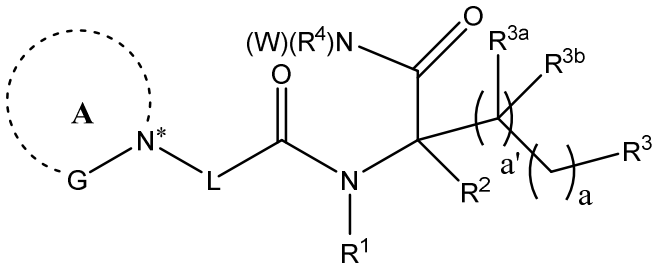
each occurrence of $\mathbf{R^e}$ is independently selected from the group consisting of: –OH; -$-N(R^a)(R'')$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; $-OC(=O)(C_{1-6}$ alkyl); $-C(=O)O(C_{1-6}$ alkyl); -C(=O)OH, $-C(=O)N(R''')(R'''')$, $-S(O)_{1-2}(C_{1-6}$ alkyl); and cyano;

each occurrence of $\mathbf{R''}$, $\mathbf{R'''}$, and $\mathbf{R''''}$ is independently selected from the group consisting of: H and C_{1-6} alkyl; and

W is a peptide having the formula W'-R^5, wherein **W'** is a sequence of from 5-60 amino acids, and $\mathbf{R^5}$ is a C-terminal amino acid, amino acid ester, or amino acid amide that is optionally substituted with from 1-2 modifying groups (e.g., 1-2 groups selected from an acyl group and a PEG group); and

provided that one or more of the compound provisions delineated herein apply.

2. The compound of claim 1, wherein the compound has formula (IA), or a pharmaceutically acceptable salt thereof:



(IA)

wherein:

ring A is:

(**i**) a saturated or unsaturated monocyclic ring that includes from 3-8 ring atoms (inclusive of **G** and the nitrogen atom labelled N*); or

(**ii**) a saturated or unsaturated bicyclic or tricyclic ring that includes from 6-14 ring atoms (inclusive of **G** and the nitrogen atom labelled N*), wherein:

- **G** is C(O), S(O), or SO_2; and
- the dotted, circular line connecting **G** and N* is a divalent group that includes from 1-6 ring atoms; wherein:

(**a**) from 0-2 of the divalent group's ring atoms are ring heteroatoms, which are each independently selected from the group consisting of N, N(**R**^{a}), O, S, and SO_2; and

(**b**) from 1-6 of the divalent group's ring atoms are ring carbon atoms, which are each independently selected from the group consisting of C, CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b;

wherein:

(**1**) when **ring A** is a monocyclic ring, then each of the divalent group's 1-6 ring carbon atoms is independently selected from the group consisting of CH, CH_2, CR^b, $C(R^b)_2$, and CHR^b; and

(**2**) when **ring A** is a bicyclic or tricyclic ring, then (**A**) or (**B**) applies:

(**A**) two or three adjacent ring carbon atoms of the divalent group are each independently selected from the group consisting of C, CH, and, CR^b and are fused to a second ring that is selected from the group consisting of:

(**a**) C_{6-10} aryl optionally substituted with from 1-5 independently selected **R**^{c};

(**b**) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N(**R**^{a}), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected **R**^{c};

(**c**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected **R**^{d};

(**d**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N(**R**^{a}), O,

and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$; or

(**B**) one of the divalent group's ring carbon atoms is C and is spiro-fused to a second ring that is selected from the group consisting of:

(**a**) C_{3-10} cycloalkyl optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**b**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

L is:

(**i**) -$(CH_2)_{\mathbf{m}}$-$\mathbf{X^1}$-$(CH_2)_{\mathbf{n}}$-$\mathbf{X^2}$-$(CH_2)_{\mathbf{p}}$- (formula VIII), wherein **m** is from 1-6; **n** is from 0-2; and **p** is from 0-8;

(**ii**) -C(O)-$(CH_2)_{\mathbf{n}}$-$\mathbf{X^3}$-$(CH_2)_{\mathbf{p}}$- (formula IX), wherein **n** is from 0-2; and **p** is from 0-8;

(**iii**) -$(CH_2)_{\mathbf{q}}$-, wherein **q** is from 1-10;

(**iv**) -C(O)-; or

(**v**) -$(CH_2)_{\mathbf{m}}$-$\mathbf{X^1}$ -$(CH_2)_{\mathbf{p}}$- (formula VIII), wherein **m** is from 1-6; and **p** is from 0-8;

$\mathbf{X^1}$ is -C(O)-; -N(R')C(O)-; -C(O)N(R')-; or -N(R')C(O)NR')-; wherein each occurrence of **R'** is independently selected from the group consisting of: H and C_{1-4} alkyl;

$\mathbf{X^2}$ is:

(**i**) -O-;

(**ii**) -S-;

(**iii**) -$S(O)_t$-, wherein **t** is 1 or 2;

(**iv**) -$C(Q^1)(Q^2)$-, wherein each of $\mathbf{Q^1}$ and $\mathbf{Q^2}$ is independently selected from the group consisting of H and C_{1-4} alkyl; or $\mathbf{Q^1}$ and $\mathbf{Q^2}$, together with the carbon atom to which each is attached forms C_{3-10} cycloalkyl that is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$ and optionally fused to phenyl;

(**v**) C_{6-10} arylene optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vi**) heteroarylene including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vii**) C_{3-10} cycloalkylene optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**viii**) heterocycloalkylene including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^d}$;

(**ix**) C_2-C_4 alkenylene optionally substituted with from 1-2 $\mathbf{R^e}$; or

(**x**) C_2-C_4 alkynylene optionally substituted with from 1-2 $\mathbf{R^e}$;

$\mathbf{X^3}$ is: -O-; -S-; or -$S(O)_t$-, wherein **t** is 1 or 2;

each of $\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^4}$ is independently selected from the group consisting of H and unsubstituted C_{1-3} alkyl;

$\mathbf{R^3}$ is -C(O)OH, -$C(O)OR^{31}$, -$CH(C(O)OH)_2$ or a carboxylic acid isostere (e.g., amide or tetrazolyl);

a is 0-5;

a' is 0 or 1;

each of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ is independently H or C_{1-3} alkyl;

$\mathbf{R^{31}}$ is:

(**i**) C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$;

(**ii**) -(C_{0-3} alkylene)-C_{3-10} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iii**) -(C_{0-3} alkylene)-heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iv**) -(C_{0-3} alkylene)-C_{6-10} aryl, wherein the aryl is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$; or

(**v**) -(C_{0-3} alkylene)-heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N(**R^a**), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected **R^c**;

each occurrence of **R^a** is independently selected from the group consisting of: H; C_{1-4} alkyl; C_{3-6} cycloalkyl; -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); and -S(O)$_{1-2}$(C_{1-6} alkyl);

each occurrence of **R^b** is independently selected from the group consisting of: **R^{31}**; C_{1-4} haloalkyl; –OH; oxo; -F; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)(C_{1-4} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of **R^c** is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected **R^e**; C_{3-6} cycloalkyl; C_{1-4} haloalkyl; –OH; -halo; -NO_2; N_3; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} thioalkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of **R^d** is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected **R^e**; C_{1-4} haloalkyl; –OH; -F; Cl; -N(R^a)(R''); oxo; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

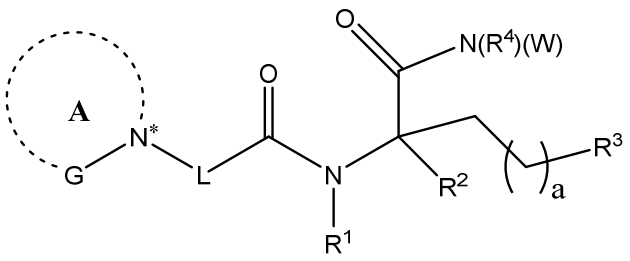
each occurrence of **R^e** is independently selected from the group consisting of: –OH; --N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of **R**", **R**"', and **R**"" is independently selected from the group consisting of: H and C_{1-6} alkyl; and

W is a peptide having the formula W'-R^5, wherein **W'** is a sequence of from 5-60 amino acids, and **R^5** is a C-terminal amino acid, amino acid ester, or amino acid amide that is optionally substituted with from 1-2 modifying groups (e.g., 1-2 groups selected from an acyl group and a PEG group); and

provided that one or more of the compound provisions delineated herein apply.

3. The compound of any one of claims 1-2, wherein the compound has formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

ring A is:

(**i**) a saturated or unsaturated monocyclic ring that includes from 3-8 ring atoms (inclusive of **G** and the nitrogen atom labelled N*); or

(**ii**) a saturated or unsaturated bicyclic or tricyclic ring that includes from 6-14 ring atoms (inclusive of **G** and the nitrogen atom labelled N*), wherein:

- **G** is C(O), S(O), or SO_2; and
- the dotted, circular line connecting **G** and N* is a divalent group that includes from 1-6 ring atoms; wherein:

(**a**) from 0-2 of the divalent group's ring atoms are ring heteroatoms, which are each independently selected from the group consisting of N, N(**R**^{a}), O, S, and SO_2; and

(**b**) from 1-6 of the divalent group's ring atoms are ring carbon atoms, which are each independently selected from the group consisting of C, CH, CH_2, CR^{b}, C(R^{b})$_2$, and CHR^{b};

wherein:

(**1**) when **ring A** is a monocyclic ring, then each of the divalent group's 1-6 ring carbon atoms is independently selected from the group consisting of CH, CH_2, CR^{b}, C(R^{b})$_2$, and CHR^{b}; and

(**2**) when **ring A** is a bicyclic or tricyclic ring, then (**A**) or (**B**) applies:

(**A**) two or three adjacent ring carbon atoms of the divalent group are each independently selected from the group consisting of C, CH, and, CR^{b} and are fused to a second ring that is selected from the group consisting of:

(**a**) C_{6-10} aryl optionally substituted with from 1-5 independently selected **R**^{c};

(**b**) heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected $\mathbf{R^c}$;

(**c**) $C_{3\text{-}10}$ cycloalkyl optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**d**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$; or

(**B**) one of the divalent group's ring carbon atoms is C and is spiro-fused to a second ring that is selected from the group consisting of:

(**a**) $C_{3\text{-}10}$ cycloalkyl optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**b**) heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

L is:

(**i**) $-(CH_2)_{\mathbf{m}}-\mathbf{X^1}-(CH_2)_{\mathbf{n}}-\mathbf{X^2}-(CH_2)_{\mathbf{p}}-$ (formula VIII), wherein **m** is from 1-6; **n** is from 0-2; and **p** is from 0-8;

(**ii**) $-C(O)-(CH_2)_{\mathbf{n}}-\mathbf{X^3}-(CH_2)_{\mathbf{p}}-$ (formula IX), wherein **n** is from 0-2; and **p** is from 0-8;

(**iii**) $-(CH_2)_{\mathbf{q}}-$, wherein **q** is from 1-10;

(**iv**) -C(O)-; or

(**v**) $-(CH_2)_{\mathbf{m}}-\mathbf{X^1}-(CH_2)_{\mathbf{p}}-$ (formula VIII), wherein **m** is from 1-6; and **p** is from 0-8;

$\mathbf{X^1}$ is -C(O)-; -N(R')C(O)-; -C(O)N(R')-; or -N(R')C(O)NR')-; wherein each occurrence of $\mathbf{R'}$ is independently selected from the group consisting of: H and $C_{1\text{-}4}$ alkyl;

$\mathbf{X^2}$ is:

(**i**) -O-;

(**ii**) -S-;

(**iii**) $-S(O)_t-$, wherein **t** is 1 or 2;

(**iv**) $-C(Q^1)(Q^2)-$, wherein each of $\mathbf{Q^1}$ and $\mathbf{Q^2}$ is independently selected from the group consisting of H and $C_{1\text{-}4}$ alkyl; or $\mathbf{Q^1}$ and $\mathbf{Q^2}$, together with the carbon atom to which each is attached forms $C_{3\text{-}10}$ cycloalkyl that is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$ and optionally fused to phenyl;

(**v**) C_{6-10} arylene optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vi**) heteroarylene including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$;

(**vii**) C_{3-10} cycloalkylene optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**viii**) heterocycloalkylene including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S; and which is optionally substituted with from 1-5 independently selected $\mathbf{R^d}$;

(**ix**) C_2-C_4 alkenylene optionally substituted with from 1-2 $\mathbf{R^e}$; or

(**x**) C_2-C_4 alkynylene optionally substituted with from 1-2 $\mathbf{R^e}$;

$\mathbf{X^3}$ is: -O-; -S-; or -$S(O)_t$-, wherein **t** is 1 or 2;

each of $\mathbf{R^1}$, $\mathbf{R^2}$, and $\mathbf{R^4}$ is independently selected from the group consisting of H and unsubstituted C_{1-3} alkyl;

$\mathbf{R^3}$ is -C(O)OH, -$C(O)OR^{31}$, or a carboxylic acid isostere; wherein $\mathbf{R^{31}}$ is:

(**i**) C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$;

(**ii**) -(C_{0-3} alkylene)-C_{3-10} cycloalkyl, wherein the cycloalkyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iii**) -(C_{0-3} alkylene)-heterocyclyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are each independently selected from the group consisting of N($\mathbf{R^a}$), O, and S, wherein the heterocyclyl is optionally substituted with from 1-4 independently selected $\mathbf{R^d}$;

(**iv**) -(C_{0-3} alkylene)-C_{6-10} aryl, wherein the aryl is optionally substituted with from 1-5 independently selected $\mathbf{R^c}$; or

(**v**) -(C_{0-3} alkylene)-heteroaryl including from 5-10 ring atoms, wherein from 1-4 ring atoms are each independently selected from the group consisting of N, N($\mathbf{R^a}$), O, and S, wherein the heteroaryl is optionally substituted with from 1-3 independently selected $\mathbf{R^c}$;

a is 0-5;

each occurrence of $\mathbf{R^a}$ is independently selected from the group consisting of: H; C_{1-4} alkyl; C_{3-6} cycloalkyl; -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); and -S(O)$_{1-2}$(C_{1-6} alkyl);

each occurrence of $\mathbf{R^b}$ is independently selected from the group consisting of: $\mathbf{R^{31}}$; C_{1-4} haloalkyl; –OH; oxo; -F; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)(C_{1-4} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of $\mathbf{R^c}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$; C_{3-6} cycloalkyl; C_{1-4} haloalkyl; –OH; -halo; -NO_2; N_3; -N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} thioalkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with from 1-2 independently selected $\mathbf{R^e}$; C_{1-4} haloalkyl; –OH; -F; Cl; -N(R^a)(R''); oxo; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

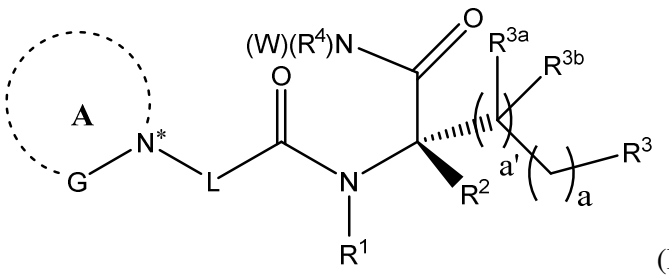
each occurrence of $\mathbf{R^e}$ is independently selected from the group consisting of: –OH; --N(R^a)(R''); C_{1-4} alkoxy; C_{1-4} haloalkoxy; -OC(=O)(C_{1-6} alkyl); -C(=O)O(C_{1-6} alkyl); -C(=O)OH, -C(=O)N(R''')(R''''), -S(O)$_{1-2}$(C_{1-6} alkyl); and cyano;

each occurrence of $\mathbf{R}$'', $\mathbf{R}$''', and $\mathbf{R}$'''' is independently selected from the group consisting of: H and C_{1-6} alkyl; and

W is a peptide having the formula W'-R^5, wherein **W'** is a sequence of from 5-60 amino acids, and $\mathbf{R^5}$ is a C-terminal amino acid, amino acid ester, or amino acid amide that is optionally substituted with from 1-2 modifying groups (e.g., 1-2 groups selected from an acyl group and a PEG group); and

provided that one or more of the compound provisions delineated herein apply.

4. The compound of any one of claims 1-2, wherein the compound has formula (IIA):



(IIA).

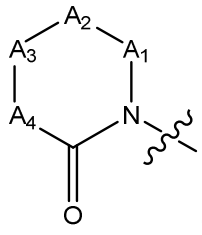
5. The compound of any one of claims 1-4, wherein **G** is C(O).

6. The compound of any one of claims 1-4, wherein **G** is S(O) or SO_2.

7. The compound of any one of claims 1-6, wherein ring A is a saturated or unsaturated monocyclic ring that includes from 3-8 (e.g., 4-8) ring atoms.

8. The compound of any one of claims 1-7, wherein ring A is a saturated monocyclic ring that includes from 3-8 (e.g., 4-8) ring atoms.

9. The compound of any one of claims 1, 2, 4, 5, and 7-8, wherein ring A has the following formula (III):



(III)

wherein:

$\mathbf{A_1}$ is a bond, $\mathbf{A^{1A}}$-$\mathbf{A^{1B}}$, C(O), CH_2, CHR^b, or $C(R^b)_2$;

each of $\mathbf{A^{1A}}$ and $\mathbf{A^{1B}}$ is independently C(O), CH_2, CHR^b, or $C(R^b)_2$;

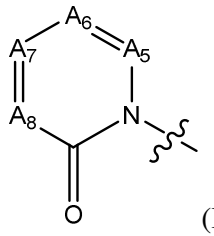
$\mathbf{A_2}$ is C(O), CH_2, CHR^b, or $C(R^b)_2$;

$\mathbf{A_3}$ is C(O), CH_2, CHR^b, or $C(R^b)_2$; O; S; SO_2, or N($\mathbf{R^a}$);

$\mathbf{A_4}$ is C(O), CH_2, CHR^b, or $C(R^b)_2$; O; S; or N($\mathbf{R^a}$); provided that $\mathbf{A_3}$ and $\mathbf{A_4}$ cannot both be O; S; or N($\mathbf{R^a}$); or a combination thereof.

10. The compound of any one of claims 1-6, wherein ring A is an unsaturated monocyclic ring that includes from 3-8 (e.g., 4-8) ring atoms.

11. The compound of claim 10, wherein ring A has formula (IV):



(IV),

wherein:

each of $\mathbf{A_6}$, and $\mathbf{A_7}$ is independently selected from CH and CR^b; and

each of $\mathbf{A_5}$ and $\mathbf{A_8}$ is independently N, CH, or CR^b.

12. The compound of any one of claims 1-6, wherein ring A is a saturated or unsaturated bicyclic or tricyclic ring that includes from 6-14 (e.g., 8-10) ring atoms.

13. The compound of any one of claims 1-6, wherein ring A is a saturated bicyclic or tricyclic ring that includes from 8-10 ring atoms.

14. The compound of any one of the preceding claims, wherein **L** has formula (VIII) : $-(CH_2)_{\mathbf{m}}-\mathbf{X^1}-(CH_2)_{\mathbf{n}}-\mathbf{X^2}-(CH_2)_{\mathbf{p}}-$.

15. The compound of any one of the preceding claims, wherein:

m is from 2-6;

$\mathbf{n + p} \geq 2$; and

$\mathbf{X^2}$ is: -O-; -S-; $-S(O)_t-$, or CH_2.

16. The compound of any one of the preceding claims, wherein:

m is 1;

$\mathbf{n + p} \leq 2$; and

$\mathbf{X^2}$ is: -O-; -S-; $-S(O)_t-$, or $C(\mathbf{Q^1})(\mathbf{Q^2})$.

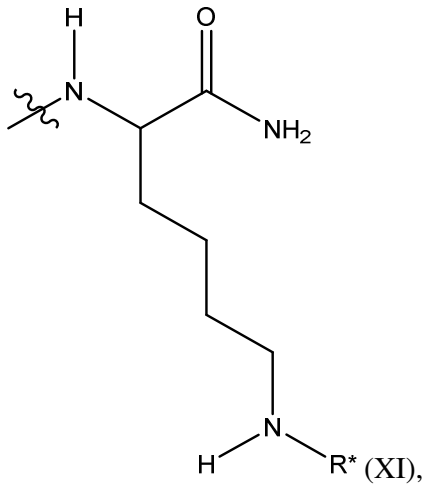
17. The compound of any one of the preceding claims, wherein **L** has formula (IX): -C(O)-$(CH_2)_{\mathbf{n}}$-$\mathbf{X^3}$-$(CH_2)_{\mathbf{p}}$-.

18. The compound of any one of the preceding claims, wherein **W** is a sequence of from 25-45 (e.g., 30-45) amino acids.

19. The compound of any one of the preceding claims, wherein **W** has formula (X): - -GTF-W''-R^5, wherein **W''** is a sequence of 30-40 (e.g., 31-36, 33) amino acids.

20. The compound of any one of the preceding claims, wherein $\mathbf{R^5}$ is a C-terminal amino acid amide that is optionally substituted with from 1-2 modifying groups (e.g., 1-2 groups selected from an acyl group and a PEG group).

21. The compound of any one of the preceding claims, wherein $\mathbf{R^5}$ has formula (XI):

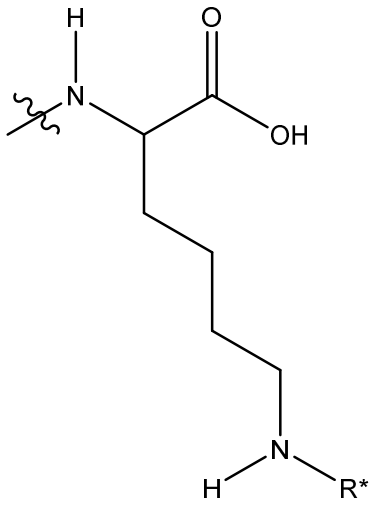


(XI),

wherein R* is H or a modifying group (e.g., an acyl group and a PEG group).

22. The compound of any one of the preceding claims, wherein $\mathbf{R^5}$ is a a C-terminal amino acid that is optionally substituted with from 1-2 modifying groups (e.g., 1-2 groups selected from an acyl group and a PEG group).

23. The compound of any one of the preceding claims, wherein **R^5** has formula (XI-OH):



(XI-OH),

wherein R* is H or a modifying group (e.g., an acyl group and a PEG group).

24. The compound of any of the preceding claims, wherein **W** is represented by SEQ ID 6.

25. The compound of claim 1, wherein the compound is selected from the group consisting of those delineated in **FIG. 1**.

26. A pharmaceutical composition comprising a compound or salt as claimed in any one of the preceding claims and one or more pharmaceutically acceptable excipients.

27. An *in vitro* method for modulating GLP-1R and/or GIPR activity, the method comprising contacting GLP-1R and/or GIPR with a compound as claimed in any one of the preceding claims.

28. Use of a compound as claimed in any one of the preceding claims in the manufacture of a medicament for modulating GLP-1R and/or GIPR activity *in vivo.*

29. Use of a compound as claimed in any one of the preceding claims in the manufacture of a medicament for modulating GLP-1R and/or GIPR induced aversion, nausea and/or vomiting.

30. Use of a compound as claimed in any one of the preceding claims in the manufacture of a medicament for modulating (e.g., increasing) insulin levels in a subject in need of such modulating.

31. Use of a compound as claimed in any one of the preceding claims in the manufacture of a medicament for modulating (e.g., decreasing) glucose levels in a subject in need of such modulating.

32. Use of a compound as claimed in any one of the preceding claims in the manufacture of a medicament for treating a disease, disorder, or condition, in which modulating GLP-1R and/or GIPR signaling can alter the pathology and/or symptoms and/or progression of the disease, disorder, or condition.

33. Use of a compound as claimed in any one of the preceding claims in the manufacture of a medicament for treating a disease, disorder, or condition, in which modulating GLP-1R and/or GIPR signaling causes aversion, nausea or vomiting.